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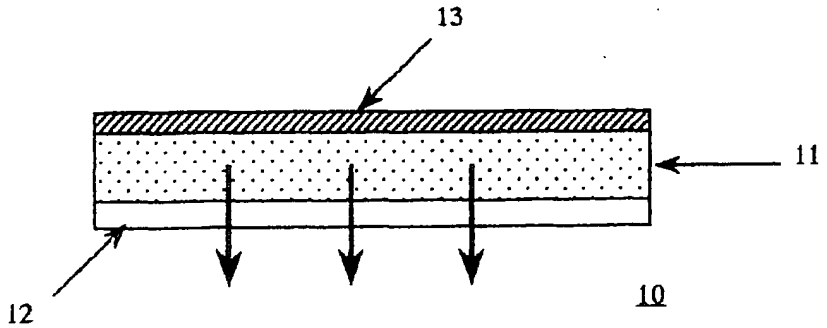
(54) Title: COMPOSITIONS AND METHODS TO EFFECT THE RELEASE PROFILE IN THE TRANSDERMAL ADMINISTRATION OF ACTIVE AGENTS



(57) Abstract: Compositions and methods for the transdermal delivery of active agents up to a period of seven days or more at substantially a zero-order release rate comprising a pharmaceutically acceptable adhesive matrix and a polymeric plastic material that provides a release rate regulating effect on the active agents.

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COMPOSITIONS AND METHODS TO EFFECT THE RELEASE PROFILE IN THE TRANSDERMAL ADMINISTRATION OF ACTIVE AGENTS

FIELD OF INVENTION

This invention relates generally to transdermal drug delivery systems, and more particularly to pharmaceutically acceptable adhesive matrix compositions, that use polymeric plastic materials, in particular insoluble cellulose derivatives such as ethyl celluloses, to regulate the drug release profile. The invention additionally relates to transdermal drug delivery systems providing substantially zero order drug release profiles for an extended period of time of up to seven days or longer.

BACKGROUND OF THE INVENTION

The use of transdermal drug delivery systems as a means to topically administer an active agent is well known. Such systems incorporate the active agent into a carrier composition, such as a polymeric and/or pressure-sensitive adhesive composition, from which the active agent is delivered through the skin or mucosa of the user.

In general, transdermal drug delivery systems are either reservoir-type or matrix-type devices. Both types of devices employ a backing layer that forms the protective outer surface of the finished transdermal system and which is exposed to the environment during use, and a release liner or protective layer that forms the inner surface and which covers whatever adhesive means is employed for affixing the system to the skin or mucosa of a user. The release liner or protective layer is removed prior to application, exposing the adhesive means, which is typically a pressure-sensitive adhesive.

In the "classic" reservoir-type device, the active agent is usually dissolved or dispersed in a carrier that typically yields a non-finite carrier form, like a fluid or gel, and which is kept separate from the adhesive means used to affix the device to the user. The device has a pocket or "reservoir" which physically serves to hold the active agent and carrier, and which is formed in or by the backing layer itself. A peripheral adhesive layer is then used to affix the device to the user. The early reservoir-type devices incorporated drugs which were readily absorbed through the skin like nitroglycerin and nicotine.

Such devices have a number of disadvantages including a non-uniform drug release profile wherein a high dose of drug is released initially upon application to the user, often described as a "burst effect." This burst or high initial release of drug then drops off after a period of time to a rate that is less than is able to achieve a therapeutically effective amount. Drug delivery according to this profile is described as first order release.

While such classic devices are still in use today, the term reservoir is being used interchangeably with matrix-type devices which still rely upon a separate adhesive means used to affix the device to the user.

In a matrix-type device, the active agent is dissolved or dispersed in a carrier that typically yields a finite carrier form, which can be self-adhesive or non-adhesive. Non-adhesive matrix-type devices, that is, those which still rely upon a separate adhesive means to affix the device to the user, employ a drug permeable adhesive layer (often referred to as an "in-line adhesive" since the drug must pass through), applied over the drug matrix carrier layer. In an attempt to better control the release rate of the drug, such devices often employ one or more additional drug permeable layers such

as rate controlling membranes, or containing excipients, such as drug delivery enhancers. Hence, such devices are also commonly referred to as multilayer or multilaminate.

In a "monolithic or monolayer"" matrix-type device, the active agent is typically solubilized or homogenously blended in an adhesive carrier composition, typically a pressure-sensitive adhesive or bioadhesive, which functions as both the drug carrier and the means of affixing the system to the skin or mucosa. Such devices, commonly referred to as drug-in-adhesive devices, are described, for example, in United States Patent Numbers 4,994,267, 5,446,070, 5,474,783 and 5,656,286, all of which are assigned to Noven Pharmaceuticals, Inc., Miami, Florida.

While matrix-type devices, especially drug-in-adhesive devices, have achieved more uniform and controlled drug deliver rates, and for longer periods of time, most transdermal systems remain subject to a higher initial drug release than is required to achieve therapeutic efficacy. For many drugs and/or therapeutic situations, it would be advantageous to eliminate or suppress this higher initial release and achieve a "steady state" (zero order) release profile which uniformly delivers a therapeutically effective amount of drug over the extended duration of device's desired use.

For example, the high initial release of certain drugs may cause adverse or undesired effects, or create toxicity concerns, thereby foreclosing the use of transdermal administration. In other instances, the higher initial release may reduce the amount of drug required for treatment to the point of risking underdosing, or may make it impractical to try and increase the duration of the device's application while retaining therapeutic effectiveness. The ability to reduce the frequency of replacing the transdermal

drug delivery system would concomitantly increase user compliance, reduce any lag or drop off in efficacious blood levels, and reduce the amount of drug required for treatment (also provided by reducing the higher initial blood level associated with the higher release rate).

Therefore, despite the existence of many different types of transdermal delivery systems in the art, there remains a continuing need for improving the release profile of drugs to achieve substantially zero order, as well as extending the duration of use of each transdermal system.

U.S. Patent Serial Number 07/897,269 discloses the use of glycerin to counteract the burst effect of drugs in transdermal formulations.

It has now been found that the addition of certain polymeric plastic polymers, in particular insoluble cellulose derivatives such as ethyl celluloses, into a pressure-sensitive adhesive matrix composition, eliminates or suppresses the initial high release rate of a drug subject to a first order release rate profile such that the system achieves substantially zero order release, and is able to maintain a substantially zero order release profile for an extended period of time up to seven days or longer.

Although not wishing to be bound by theory, particularly in this case where the structure of the composition has not been analyzed, it is postulated that the insoluble polymeric plastic material affects the uptake/absorption of water or moisture from the application site into the matrix composition which would otherwise create some of the kinetic driving force for release of the drug. This appears especially significant in the presence of hydrophobic drugs and/or in conjunction with the use of hydrophilic crystallization inhibitors, such as polyvinylpyrrolidones.

Ethyl celluloses have been extensively used in industrial applications since their commercial introduction in the mid-1930s. They are recognized and widely used as well for many different purposes in pharmaceutical applications, especially in conjunction with water-sensitive ingredients. Ethyl celluloses are most frequently used as binders, fillers, flavor fixatives, controlled release coatings/barriers in microencapsulation and other solid dosage forms, particularly multiparticulate systems, granulation aids, tablet film formers and taste maskers.

The prior art generally discloses the use of insoluble polymers such as ethyl cellulose as optional components in transdermal systems as thickening agents and as cohesiveness strengthening agents which effect the carrier's adhesive properties. For example, U.S. Patent No.5,232,702 discloses the use of a variety of substances that include ethyl cellulose and polyvinyl alcohol as cohesive strengthening agents (reducing flow properties of silicone adhesives) in a transdermal delivery system.

The present invention is able to regulate the release profile of the drug in a transdermal system without modifying the adhesive properties of the pressure-sensitive adhesive matrix so that the transdermal system possesses the required degree of adhesion and tackiness to remain affixed to the site of application for extended periods of time, which can be seven days or more, but at the same time can be easily removed as required.

The prior art further generally discloses the use of insoluble polymers in transdermal systems as the non-adhesive matrix carrier itself, and even as a "suitable adhesive" for the matrix carrier itself (but which presumably includes the addition of a plasticizer or tackifier, or plasticizing liquid drug like nicotine, to create stickiness since such polymers

are not adhesives). For example, U.S. Patent No. 6,010,715 discloses the use of thermoplastic polymers that are melt-blended with active agents and enhancers that are heat stable at the melt temperature of the polymer. The melt-blend can then be thermoformed into carrier layers without the use of common solvents to produce a controlled release layer in a transdermal drug delivery system. Cellulose derivatives such as ethyl cellulose are generally disclosed as "suitable adhesives" for use as the matrix.

U.S. Patent No. 5,904,931 discloses the use of ethyl cellulose as a crystallization inhibitor in a transdermal drug delivery system. Cellulose ether and polyvinyl compounds are generally described as additional matrix additives.

SUMMARY OF THE INVENTION

It is therefore an objective of the present objective to provide for methods and pharmaceutically acceptable flexible, finite compositions and systems for the transdermal administration of active agents that achieve a substantially zero-order release profile when applied to a user.

It is another object of the invention to provide an adhesive matrix-type transdermal drug delivery system which achieves a substantially zero-order release profile of the active agent by incorporating a polymeric plastic material into an adhesive drug matrix.

It is still another object of the invention to achieve a substantially zero-order release profile of the active agent for an extended period of time of up to seven days or longer, and effectively continue to deliver the active agent in a therapeutically effective amount.

It is a further object of the invention to provide a method of eliminating or suppressing the high initial release

or burst of active agent from an adhesive matrix type transdermal drug delivery system containing a drug subject to a first order release profile.

It is yet another object of the invention to provide a transdermal drug delivery system that can deliver an active agent at substantially zero-order for an extended period of time in excess of 72 hours and up to seven days or more without substantially increasing the surface area of the transdermal delivery system.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a schematic illustration of a matrix-type transdermal drug delivery system of the present invention.

FIG. 2 is a graphical representation comparing the in vitro flux rate of estradiol and norethindrone acetate through cadaver skin from a pressure-sensitive adhesive matrix composition of the present invention with the flux rate for a composition of the prior art.

FIG. 3 is a graphical representation of the in vitro first order flux rate of estradiol through cadaver skin from a transdermal drug delivery system of the prior art as compared to the in vitro steady state flux rate of estradiol through cadaver skin from an transdermal drug delivery system of the present invention.

FIG. 4 is a graphical representation of the in vitro flux rates of estradiol through cadaver skin from two pressure-sensitive adhesive matrix compositions of the present invention using various amounts of ethyl cellulose as compared to the in vitro flux rate of estradiol from a pressure-sensitive adhesive matrix composition without ethyl cellulose.

FIG. 5 is a graphical representation of the in vitro flux rates of estradiol through cadaver skin from pressure-

sensitive adhesive matrix compositions of the present invention comparing the effect of varying amounts of ethyl cellulose with varying amounts of estradiol.

FIG. 6 is a graphical representation of the in vitro flux rates of estradiol and norethindrone acetate through cadaver skin from pressure-sensitive adhesive matrix compositions comparing the effect of using a combination of ethyl cellulose and cellulose acetate butyrate versus either polymer alone.

DETAILED DESCRIPTION OF THE INVENTION

The foregoing and other objects are achieved by this invention which provides a transdermal drug delivery system wherein the use of a polymeric plastic material provides a release rate regulating effect on the active agents incorporated into the adhesive matrix composition.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

The term "topical" or "topically" is used herein in its conventional meaning as referring to direct contact with an anatomical site or surface area on a mammal including skin, teeth, nails and mucosa.

The term "mucosa" as used herein means any moist anatomical membrane or surface on a mammal such as oral, buccal, vaginal, rectal, nasal or ophthalmic surfaces.

The term "transdermal" as used herein means passage into and/or through skin or mucosa for localized or systemic delivery of an active agent.

The term "solubilized" is intended to mean that in the carrier composition there is an intimate dispersion or dissolution of the active agent at the crystalline, molecular

or ionic level. As such, the active agent is considered herein to be in "non-crystallized" form when in the compositions of the present invention.

As used herein, the term "flux" is defined as the absorption of the drug through the skin or mucosa, and is described by Fick's first law of diffusion:

$$J=-D\ (dCm/dx),$$

Where J is the flux in g/cm2/sec, D is the diffusion coefficient of the drug through the skin or mucosa in cm2/sec and Dcm/dx is the concentration gradient of the drug across the skin or mucosa.

The phrase "pharmaceutically acceptable flexible, finite" is intended to mean a solid form capable of conforming to a surface to which it is applied, and which is capable of maintaining the contact in such solid form so as to facilitate topical application without adverse physiological response, and without being appreciably decomposed by aqueous contact during use by a subject.

The term "user" or "subject" is intended to include all warm-blooded mammals, preferably humans.

The phrase "substantially zero-order" as used herein means transdermal delivery of an active agent at a release rate which is approximately constant once steady state is attained, typically within 12 to 24 hours after topical application. While variability in blood levels of active agent are contemplated within the scope of this meaning once steady state release is attained, the depletion rate of active agent over the duration of use should typically not exceed about 20% to about 25%.

Any polymeric plastic material may be employed for the present invention provided it is insoluble or substantially insoluble in water, and includes cellulose derivatives such as cellulose acetates, (cellulose acetate butyrate, cellulose

acetate propionate, cellulose acetate phthalate, etc.), methyl, ethyl and propyl celluloses; polycarbonates; polystyrenes; alkylacrylates such as polymethyl methacrylate, polyethyl ethacrylate, polyethylene methacrylate and other lower alkyl acrylates; vinyl polymers; polyurethanes; polyacrylonitriles; and mixtures, combinations and multipolymers (copolymers, terpolymers, etc.) thereof.

In preferred embodiments, the polymeric plastic material is a cellulose derivative. Preferred are cellulose esters such as cellulose acetates including cellulose acetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate propionate, and cellulose ethers. Particularly preferred are cellulose acetate butyrates, such as CAB-381-0.1, CAB-381-0.5 and CAB-553-0.4, and cellulose acetate propionates, which are all commercially available from Eastman Chemical Products, Inc., Kingsport, Tennessee.

Copending provisional application, Serial No. 60/137,827, describes the use of cellulose derivatives, particularly cellulose esters, as drug solubility enhancers in matrix carrier compositions.

Particularly preferred cellulose ethers are ethyl cellulose polymers. Ethyl cellulose polymers can be manufactured in a variety of molecular weights, which translates into a range of viscosities when in solution. In practicing the subject invention, it has been found that solution viscosities ranging from about 3 centipoise to about 49 centipoise are preferred, and more preferably from about 6 centipoise to about 40 centipoise, and optimally from about 6 centipoise to about 22 centipoise (viscosities are for 5% solutions, in 80% toluene and 20% ethanol, measured at 25°C in an Ubbelohde viscometer). Ethyl cellulose polymers having such solution viscosities exhibit melting point temperatures in the range of about 165°C to about 200°C. Suitable ethyl

cellulose polymers are commercially available and include those sold under the trademark ETHOCEL® by the Dow Chemical Company, Midland, Michigan. Preferred ETHOCEL® polymers are ETHOCEL Standard 4, 7, 10, 14 and 20, Premium or Industrial grades.

A crystallization inhibitor or solubility enhancer may also be employed in the invention, for example polyvinylpyrrolidone polymers, polyethylene oxide, polyacrylic acid, polyvinyl alcohol, silicone dioxide, silica, celluloses and cellulose derivatives such as hydroxymethyl cellulose, hydroxypropyl cellulose, gelatins, gums, starches, dextrins and dextrans, sterols, bile acids and other absorptive agents that possess the capability to absorb and hold water or moisture.

Particularly preferred compounds are PVPs. The term "polyvinylpyrrolidone" or "PVP" refers to a polymer, ether a homopolymer or copolymer, containing vinylpyrrolidone (also referred to as N-vinylpyrrolidone, N-vinyl-2-pyrrolidone and N-vinyl-2-pyrrolidinone) as a monomeric unit. PVP polymers include soluble and insoluble homopolymeric PVPs, and copolymers such as vinylpyrrolidone/vinyl acetate and vinylpyrrolidone/dimethylamino-ethylmethacrylate. The cross-linked hompolymer (such as KOLLIDON® CL from BASF) is insoluble and is generally known in the pharmaceutical industry under the designations polyvinylpolypyrrolidone, crospovidone and PVP. The copolymer vinylpyrrolidone-vinyl acetate is generally known in the pharmaceutical industry under the designations Copolyvidon (e), Copolyvidonum or VP-VAc.

Particularly preferred PVPs are soluble. The term "soluble" when used with reference to PVP means that the polymer is soluble in water and generally is not substantially cross-linked, and has a molecular weight of less than about 2,000,000. See, generally, Bűhler, KOLLIDON®:

POLYVINYLPRYRROLIDONE FOR THE PHARMACEUTICAL INDUSTRY, BASF Aktiengesellschaft (1992). Soluble PVP polymers have been identified in the pharmaceutical industry under a variety of names, the most commonly used include Povidone, Polyvidon (e), Polyvidonum, poly (N-vinyl-2-pyrrolidinone, poly (N-vinylbutyrolactam), poly (1-vinyl-2-pyrrolidinone, poly [1-(2-oxo-1pyrrolidinyl)ethylene].

The amount and type of PVP required in the preferred embodiments will depend on the quantity and type of drug present in the adhesive matrix composition, as well as the type of adhesives, but can be readily determined through routine experimentation.

Typically, the PVP is present in an amount from about 5% to about 50% by weight, preferably from about 10% to about 40% by weight based on the dry weight of the total adhesive matrix composition. However, the amount of PVP can be higher than 20% for example, up to 40%, depending on the particular drug used and on the desired properties of the matrix blend.

Said PVP preferably has a molecular weight of about 2,000 to 2,000,000, more preferably 5,000 to 100,000, and most preferably 7,000 to 54,000. PVP having a molecular weight of about 1,000,000 to about 1,500,000 is also preferred.

PVPs are sold to the pharmaceutical industry under the trademarks KOLLIDON by BASF (Parsippanny, New Jersey); PLASDONE, POLYPLASDONE and COPOLYMER 958 by ISP Technologies, Wayne, New Jersey. Preferred PVPs are KOLLIDON 12PF, 17PF, 25, 30, 90 and VA-64.

Particularly preferred embodiments of the invention include soluble PVP in a polyacrylate and polysiloxane pressure-sensitive adhesive matrix blend.

The amount and type of polymeric plastic material required in the practice of the invention will depend on the one or more additional materials used in the adhesive matrix

composition, and on the amount and type of active agent(s). Generally, the amount of polymeric plastic material to be used is an amount sufficient to deliver a therapeutically effective amount of the active agent at a substantially zero-order kinetic rate of delivery for an extended period of time of at least three days and up to seven days or longer, and to eliminate or suppress the high initial release rate of a drug subject to a first order release profile. Typically, the amount of polymeric plastic material to be used ranges from about 0.5% to about 30%, preferably from about 2.5% to 20%, and more preferably from about 5.0% to 15% by weight based on the dry weight of the total adhesive matrix composition. Amounts greater than 30% typically result in loss of adhesive properties necessary to maintain the system topically for an extended period of time.

The adhesive matrix compositions of the present invention are designed to effectively deliver an active agent in a therapeutically effective amount for an extended period of time up to seven days or longer. As used herein, "therapeutically effective" means an amount of an active agent that is sufficient to achieve the desired local or systemic effect or result, such as to prevent, cure, diagnose, mitigate or treat a disease or condition, when applied topically over the duration of intended use. Seven days is generally the preferred maximum duration for application of a transdermal drug delivery system of the present invention because the site of application is typically adversely affected when occluded for a period of time greater than seven days. However, if a non-occlusive backing material (i.e., permeable to water vapor and/or oxygen) is used, then the transdermal system may be applied for periods longer than seven days without adverse effects occurring, if at all, until a much later time. While delivery of drug by the present invention is preferred for at

least a seven-day continuous application, the transdermal system may be used discontinuously (i.e., replaced at any time during rather than at the end of the intended duration of use) since the drug release profile is substantially zero order.

The term "active agent" (and its equivalents "agent," "drug," "medicament" and "pharmaceutical") is intended to have the broadest meaning and includes at least one of any therapeutic, prophylactic, pharmacological or physiological active substance, cosmetic and personal care preparations, and mixtures thereof, which is delivered to a mammal to produce a desired, usually beneficial, effect. More specifically, any active agent that is capable of producing a pharmacological response, localized or systemic, irrespective of whether therapeutic, diagnostic, cosmetic or prophylactic in nature, is within the contemplation of the invention. It should be noted that the active agents can be used singularly or in combinations and mixtures.

There is no limitation on the type of active agent that can be used in this invention. However, active agents that are solid or crystalline at room temperature are preferred over liquid drugs, especially nicotine. Moreover, drug forms other than the free base form are also preferred.

The active agents contained in the adhesive matrix composition can be in different forms such as pharmaceutically acceptable salts, bases, esters, amides or pro-drugs, or may be modified by appending one or more appropriate functionalities to enhance selected physical or biological properties, for example as neutral molecules, components of molecular complexes or free bases to improve solubility or release characteristics; or as pharmaceutically acceptable ethers, esters, amides and the like which have desirable retention and release characteristics but which are easily metabolized at body pH.

Compounds may be converted into pharmaceutically acceptable salts, and the salts may be converted into pharmaceutically acceptable free compound using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th Ed. (New York: Wiley-Interscience, 1992). Acid addition salts are prepared from the free base (e.g., compounds having a neutral $-NH_2$ or cyclic amine group) using conventional means, involving reaction with a suitable acid. An acid addition salt may be converted to the free base by treatment with a suitable base. Basic salts of acid moieties which may be present (e.g., carboxylic acid groups) can be prepared in a similar manner using pharmaceutically acceptable inorganic or organic bases. Compounds may also be converted into pharmaceutically acceptable esters. Suitable esters include branched or unbranched, saturated or unsaturated C_1 to C_6 alky esters, for example, methyl, ethyl and vinyl esters. Preparation of esters involves functionalization of hydroxyl and/or carboxyl groups which may be present. Pharmaceutically acceptable esters may be prepared using methods known to those skilled in the art and/or described in the pertinent literature. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures. Preparation of amides and pro-drugs can be performed in an analogous manner.

Steroids and hormonal active agents (including both natural, semi-synthetic and synthetic compounds and their derivatives having steroidal or hormonal activity) are preferred and include, for example, (a) estrogens such as Colpormon, Conjugated Estrogens, Estradiol (17β- and α-) and its Esters (e.g., Acetate, Benzoate, Cypionate, Dipropionate Diacetate, Enanthate, Estradiol-16,17-Hemisuccinate,

Undececenoate, Undecylate and Valerate), Estriol, Estrone, Ethinyl Estradiol, Equilenin, Equilin, Mestranol, Methyl Estradiol, Moxestrol, Mytatrienediol, Quinestradiol, Quinestrol, Dienestrol, Clomifen, Chlorotrianisen, and Cyclofenil; (b) progestagenically effective hormones such as Allylestrenol, Anagestone, Chlormadinone Acetate, Delmadinone Acetate, Demegestone, Desogestrel, 3-Keto Desogestrel, Dimethisterone, Dydrogesterone, Ethinylestrenol, Ethisterone, Ethynodiol (and Diacetate), Flurogestone Acetate, Gestodene, Gestonorone Caproate, Haloprogesterone, (17-Hydroxy- and 17-Acetate-) 16-Methylene-Progesterone, 17α-Hydroxyprogesterone (Acetate and Caproate), Levonorgestrel, Lynestrenol, Medrogestone, Medroxyprogesterone (and Acetate), Megestrol Acetate, Melengestrol, Norethindrone (Acetate and Enanthate), Norethisterone, Norethynodrel, Norgesterone, Norgestimate, Norgestrel, Norgestrienone, 19-Norprogesterone, Norvinisterone, Pentagestrone, Progesterone, Promegestone, Quingestrone and Trengestone; and (c) androgenically effective hormones such as Aldosterone, Androsterone, Boldenone, Cloxotestosterone, Dehydroepiandrosterone, Fluoxymesterone, Mestanolone, Mesterolone, Methandrostenolone, Methyltestosterone, 17α-Methyltesteosterone, 17α-Methyltestosterone 3-Cyclopentyl Enol Ether, Norethandrolone, Normethandrone, Oxandrolone, Oxymesterone, Oxymetholone, Prasterone, Stanlolone, Stanozolol, Testosterone (Acetate, Enanthate, Isobutyrate, Propionate and Undecanoate), Testosterone 17-Chloral Hemiacetal, Testosterone 17ß-Cypionate and Tiomesterone.

The adhesive matrix composition of the invention preferably contains 17ß-estradiol or ethinyl estradiol as the estrogen alone, or in combination with, Norethindrone (Acetate and Enanthate) or Norethisterone, as the progestagen, and mixtures thereof.

In embodiments containing combinations and mixtures of estrogens and progestagens, the use of combinations and mixtures of cellulose derivatives, particularlly cellulose esters and ethers, provide improved drug release profiles for an extended period of time as compared to an adhesive matrix composition containing either one alone or none. Preferred combinations or mixtures of cellulose esters and ethers are ethyl cellulose with cellulose acetate butyrate or with cellulose acetate propionate. When used in combinations and mixtures, the amount of each such polymer typically ranges from about 2.5% to about 10% by weight based on the dry weight of the total adhesive matrix composition. Particularly preferred embodiments of such mixtures and combinations include soluble PVP, and typically in an amount of about 5% to about 15% by weight based on the dry weight of the total adhesive matrix composition.

As shown in FIG. 6, in pressure-sensitive adhesive matrix compositions containing both 17β-estradiol (E_2) and norethindrone acetate (NETA) in a polyacrylate/polysiloxane adhesive blend with 10% PVP, Formula 4 comprising 5.0% ethyl cellulose and 5.0% cellulose acetate butyrate demonstrated an improved release profile as compared to either Formula 1 (only 10% PVP), Formula 2 (5.0% ethyl cellulose) or Formula 3 (5.0% cellulose acetate butyrate). The foregoing formulas were prepared using the method of Example 1 to yield the following ingredient concentrations set forth in tabular form in TABLE I.

TABLE I

	Formula 1	Formula 2	Formula 3	Formula 4
Polysiloxane Adhesive (BIO-PSA® 7-4603)	71.3	60.0	60.0	55.0
Polyacrylate Adhesive (DURO-TAK® 87-2287)	0.0	5.0	5.0	5.0
Polyacrylate Adhesive (Gelva® 737)	5.0	0.0	0.0	0.0
Ethyl Cellulose (Ethocel® 10)	0.0	5.0	0.0	5.0
Cellulose Acetate Butyrate (CAB-381-0.5)	0.0	0.0	5.0	5.0
Polyvinylpyrrolidone (KOLLIDON® 30)	10.0	10.0	10.0	10.0
Oleic Acid	6.0	0.0	0.0	0.0
Dipropylene Glycol	4.0	9.0	9.0	9.0
Oleyl Alcohol	0.0	6.0	6.0	6.0
Estradiol	0.7	1.0	1.0	1.0
Norethindrone Acetate	3.0	4.0	4.0	4.0

Other specific drugs for which the invention can be particularly usefully employed include α-Adrenergic Agonist agents such as Phenylpropanolamine and Talipexole; α-Adrenergic Blockers; Alcohol Deterrents; Aldose Reductase Inhibitors; Anabolics; Analgesics and/or Anti-Migraine agents such as Acetaminophen, Acetylsalicylic Acid, Buprenorphine, Codeine, Fentanyl, Hydomorphone, Lisuride, Salicylic Acid derivatives, Sufentanil and Sumatriptan; Anesthetic agents such as Benzocaine, Bupivicaine, Cocaine, Dibucaine, Dyclonine, Etidocaine, Lidocaine, Mepivacaine, Prilocaine, Procaine and Tetracaine; Anoretic agents such as Fenfluramine, Mazindol and Phentermine; Anthelmintics; Antiacne; Anti-Allergic agents such as Amlexanox, Astemizole, Azelastine, Cromolyn, Fenpiprane, Ibudilast, Nedocromil, Oxatomide, Pentigetide, Repirinast, Tranilast and Traxanox; Antiamebics;

Antiandrogens; Antianginals; Antiarrhythmics; Antiarteriosclerotics; Antiarthritic/Antirheumatics; Anti-Bacterial and Antibiotic agents including Aminoglycosides, ß-Lactams, Cephamycins, Macrolides, Penicillins, Polypeptides and Tetracyclines; Anti-Cancer agents such as Aminolevulinic Acid, 5-Fluouracil, Methotrexate, Rufocromomycin, Sulfosamide, Tamoxifen and Taxol; Anti-Cholinergic agents such as Atropine, Eucatropine and Procyclidine; Anticonvulsants; Antidepressants; Anti-Diabetic agents such as Glipizide, Glyburide, Glypinamide, Insulins, Repaglinide, Rosiglitazone and Troglitazone; Antidiarrheal; Antidiuretics; Anti-Emetic agents such as Acetylleucine Monoethanolamine, Alizapride, Benzquinamide, Bietanautine, Bromopride, Buclizine, Chlorpromazine, Clebopride, Cyclizine, Dimenhydrinate, Dipheniodol, Domperidone, Granisetron, Meclizine, Methalltal, Metoclopramide, Metopimazine, Nabilone, Ondansteron, Oxypendyl, Pipamazine, Piprinhydrinate, Prochlorperazine, Scopolamine, Tetrahydrocannabinols, Thiethylperazine, Thioproperzaine, Trimethobenzamide and Tropisetron; Antiestrogens; Anti-Fungal agents such as Clortrimazole, Ketoconazole, Miconazole, Nystatin and Triacetin; Antigonadotropins; Antigout agents; Antihistamine agents such as Tricyclics such as Ahistan, Etymemazine, Fenethazine, N-Hydroxyethylpromethazine Chloride, Isopromethazine, Mequitazine, Promethazine, Pyrathiazine, and Thiazinamium Methyl Sulfate, and Loratadine and Clobenzepam; Anti-Hyperlipoproteinemic agents such as Atorvastatin, Cerivastatin, Lovastatin, Pravastatin and Simvastatin; Antihypertensive; Anti-Hyperthyroid agents such as Methimazole; Antihypotensive agents; Antihypothyroid agents; Anti-Inflammatory and/or Corticoid agents (steroidal and non-steroidal) such as Beclomethasone, Betamethasone (and Acetate, Diproprionate and Valerate), Corticosterone, Cortisone,

Deoxycortocosterone (and Acetate), Dexamethasone, Diclofenac, Fenoprofen, Flucinolone (and Acetonide), Fludrocortisone, Fluocinonide, Flunisolide, Fluradrenolide, Flurbiprofen, Halcinonide, Hydrocortisone (and Acetate), Ibuprofen, Ibuproxam, Indoprofen, Ketoprofen, Ketorolac, Naproxen, Nimesulide, Oxametacine, Oxyphenbutazone, Piroxicam, Prednisolone, Prednisone, Suprofen and Triamcinolone (and Acetonide); Anti-Malarial agents such as Pyrimethamine; Antinauseant agents; Anti-Parkinson's and/or Anti-Alzhiemer's agents such as Biperiden, Bromocriptine, Cabergoline, 1-Hydroxy-Tacrine, Levodopa, Lisuride, Pergolide, Pramipexole, Quinpirole, Ropinirole, Rivastigmine, Physostigimine, Selegiline (Deprenyl and L-Deprenyl), Tacrine and Teruride; Antipheochromocytoma drugs; Antipneumocystis drugs; Antiprostatic hypertrophy drugs; Antiprotozoal drugs; Antipuritics; Antipsoriatic drugs; Anti-Psychotic and/or Anti-Anxiety and/or Anti-Depressant agents such as Acetophenazine, Bromperidol, Chlorproethazine, Chlorpromazine, Clomipramine, Clozapine, Fluoxetine, Fluphenazine, Haloperidol, Loxapine, Mesoridazine, Molindone, Paroxetine, Perphenazine, Piperacetazine, Sertraline, Thiopropazate, Thioridazine, Thiothixene, Trifluoperazine, Triflupromazine and Venlafaxine; Antipyretics; Antirickettsial drugs; Antispasmodic drugs; Antithrombotic drugs; Antitussive drugs; Anti-Ulcerative agents such as Enprostil and Misoprostol; Anti-Viral agents such as Acyclovir, Rimantadine and Vidarabine; Anxiolytic agents such as Azapirones such as Buspirone and Ipsapirone, Benzodiazepines such as Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Flurazepam, Halazepam, Lorazepam, Oxazepam, Oxazolam, Prazepam and Triazolam, and Carbamates; ß-Adrenergic agonist agents such as Albuterol, Carbuterol, Fenoterol, Metaproterenol, Mirtazapine, Rimiterol, Quinterenol, Salmefamol, Soterenol, Tratoquinol, Terbutaline

and Terbuterol; ß-Adrenergic blockers; Bronchodilators such as Ephedrine derivatives including Epiniphrine and Isoproterenol, Albuterol, Salbutanol, Clenbuterol and Theophylline; Calcium channel blockers; Calcium regulators; Cardioactive agents such as Atenolol, Benzydroflumethiazide, Bendroflumethiazide, Calcitonin, Captopril, Chlorothiazide, Clonidine, Clopamide, Dobutamine, Dopamine, Diltiazem, Enalapril, Enalaprilat, Fenoldopam, Gallopamil, Indomethacin, Isosorbide (Dinitrate and Mononitrate), Monoxidil, Nicardipine, Nifedipine, Nitroglycerin, Papaverine, Prazosin, Procainamide, Propranolol, Prostaglandin (E_1 and E_2), Quinidine Sulfate, Timolol, and Verapamil; Central Nervous System stimulants and agents such as Dextroamphetamine, Methylphenidate (and each Enantiomer and Free Base Form) and Nicotine; Choleretics; Cholinergic agents such as Acetylcholine, Arecoline, Bethanechol, Carbachol, Choline, Methacoline, Muscarine and Pilocarpine; Dental agents such as Bisphosphonates and Caries Prophylactics; Diuretics; Dopamine Receptor Agonist agents; Enzymes and Peptides; Estrogens (non-steroidal); Glucocorticoids; Gonad-Stimulating Principles; Gonadotropic Hormones; Growth Hormone Inhibitors; Growth Hormone Releasing Factors; Growth Stimulants; Immunomodulators; Immunosuppressants; Lactation Stimulating Hormone; LH-RH Agonists; Lipotropic agents; Lupus Erythematosus Suppressants; Mineralcorticoids; Miotic drugs; Monoamine Oxidase Inhibitors; Mucolytic agents; Muscle Relaxants such as Baclofen; Narcotic Antagonist agents such Nalmfene and Naloxone; Neuroprotective agents; Nootropic agents; Ovarian Hormone; Oxytocic drugs; Pepsin Inhibitors; Peristaltic Stimulants; Prolactin Inhibitors; Prostaglandins and Prostaglandin Analogs; Protease Inhibitors; Respiratory Stimulants; Sclerosing agents; Sedatives and Hypnotics; Thrombolytic agents; Thyrotropic Hormones; Uricosurics; Vasodilators (cerebral and coronary);

Vasoprotectants; Vitamins, Vitamin Sources, and Vitamin Extracts; Vulnerary agents; Anticoagulants; and Miscellaneous such as Erythropoietin (Hematinic), Filgrastim, Finasteride (Benign Prostate Hypertrophy), Interferon Beta 1 - Alpha (Multiple Sclerosis), Tretinonin (Urinary Incontinence), Sildenafil (Impotency) and Recalcine.

The amount of active agent to be incorporated in the carrier composition will vary depending on the particular active agent, the desired therapeutic effect, and the time span for which the transdermal system is to provide therapy. Normally, the amount of active agent in the transdermal system can vary from about 0.1% to about 50%, and preferably from about 0.1% to about 30% by weight based on the dry weight of the total adhesive matrix composition. For lower dose concentrations permitted by this invention, such as with steroids and hormones, the preferred amount is from about 0.1% to about 10%.

While not essential, it is preferred that the androgenic hormones be incorporated near, at or above saturation with respect to its concentration in the adhesive matrix composition.

The term "adhesive matrix composition" as used herein refers to any non-aqueous adhesive material into which an active agent is solubilized or homogeneously blended either without, or in combination or admixture with, other ingredients useful for facilitating transdermal drug delivery, such as crystallization inhibitors, solubility enhancers, permeation enhancers, solvents, co-solvents and other types of additives. An "adhesive" as used herein means any natural or synthetic material that is capable of sticking to the site of topical application. The term "pressure-sensitive adhesive" as used herein refers to an adhesive which adheres instantaneously to most surfaces with the application of very

slight pressure and remains permanently tacky. An adhesive is a pressure-sensitive adhesive within the meaning of that term as used herein if it has the properties of an adhesive pressure-sensitive adhesive *per se* or functions as the same by admixture with tackifiers, plasticizers, cross-linking agents or other additives.

Suitable adhesives include all of the non-toxic natural and synthetic polymers known for or suitable for use in transdermal devices as adhesives including acrylic polymers, gums, silicone-based polymers (broadly referred to as "polysiloxanes") and rubber-based adhesives such as polyisobutylenes, polybutylenes, ethylene/vinyl acetate and vinyl acetate based adhesives, styrene/butadiene adhesives, polyisoprenes, styrenes and styrene block copolymers and block amide copolymers.

Suitable polysiloxanes include silicone pressure-sensitive adhesives which are based on two major components: a polymer, or gum, and a tackifying resin. The polysiloxane adhesive is usually prepared by cross-linking the gum, typically a high molecular weight polydiorganosiloxane, with the resin, to produce a three-dimensional silicate structure, via a condensation reaction in an appropriate organic solvent. The ratio of resin to polymer is the most important factor which can be adjusted in order to modify the physical properties of polysiloxane adhesives. Sobieski, *et al.*, "Silicone Pressure Sensitive Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

Further details and examples of silicone pressure-sensitive adhesives which are useful in the practice of this invention are described in the following U.S. Patents: 4,591,622; 4,584,355; 4,585,836; and 4,655,767.

Suitable silicone pressure-sensitive adhesives are commercially available and include the silicone adhesives sold under the trademarks BIO-PSA® by Dow Corning Corporation, Medical Products, Midland, Michigan.

In particularly preferred embodiments of the invention, the adhesive matrix composition comprises a pressure-sensitive adhesive, and more preferably a blend of one or more pressure-sensitive acrylic polymers and polysiloxanes.

The term "acrylic polymer" is intended to be used interchangeably with the terms acrylate polymer, polyacrylate and polyacrylic adhesive polymers as used herein and as known in the art.

The acrylic polymers useful in practicing the invention are polymers of one or more monomers of acrylic acids and other copolymerizable monomers. The acrylic polymers also include copolymers of alkyl acrylates and/or methacrylates and/or copolymerizable secondary monomers or monomers with functional groups. By varying the amount of each type of monomer added, the cohesive properties of the resulting acrylic polymer can be changed as is known in the art. In general, the acrylic polymer is composed of at least 50% by weight of an acrylate or alkyl acrylate monomer, from 0 to 20% of a functional monomer copolymerizable with the acrylate, and from 0 to 40% of other monomers.

Acrylate monomers which can be used include acrylic acid, methacrylic acid, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, 2-ethylbutyl acrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate, and tridecyl methacrylate.

Functional monomers, copolymerizable with the above alkyl acrylates or methacrylates, which can be used include acrylic acid, methacrylic acid, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitrile, dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate, tert-butylaminoethyl methacrylate, methoxyethyl acrylate and methoxyethyl methacrylate and other monomers having at least one unsaturated double bond which participates in copolymerization reaction in one molecule and a functional group on its side chain such as a carboxyl group, a hydroxyl group, a sulfoxyl group, an amino group, an amino group and an alkoxyl, as well as a variety of other monmeric units including alkylene, hydroxy-substituted alkylene, carboxylic acid-substituted alkylene, vynylalkanoate, vinylpyrrolidone, vinylpyridine, vinylpirazine, vinylpyrrole, vinylimidazole, vinylcaprolactam, vinyloxazole, vyinlacate, vinylpropionate and vinylmorpholine.

Further details and examples of acrylic adhesives which are suitable in the practice of the invention are described in Satas, "Acrylic Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

Suitable acrylic adhesives are commercially available and include the polyacrylate adhesives sold under the trademarks DURO-TAK® by National Starch Company, Bridgewater, New Jersey; GELVA® by Solutia, St. Louis, Missouri; HRJ by Schenectady International, Inc., Chicago, Illinois; and EUDRAGIT® by Roehm Pharma GmbH, Darmstadt, Federal Republic of Germany.

The amount of the adhesive to be used depends on the concentration of active agent used to achieve a therapeutic effect. Typically, the adhesive is in an amount of about 5% to about 90%, and preferably about 10% to about 90%, and most

preferably about 20% to about 75% by weight based on the dry weight of the total adhesive matrix composition.

The adhesive matrix compositions of the present invention can also contain one or more solvents and/or co-solvents. Such solvents and/or co-solvents are those known in the art, and are non-toxic, pharmaceutically acceptable substances, preferably liquids, which do not substantially negatively affect the adhesive properties of the transdermal system or the solubility of the active agents at the concentrations used. The solvent and/or co-solvent can be for the active agent or for the matrix materials, or both.

Suitable solvents include volatile liquids such as alcohols (e.g., methyl, ethyl, isopropyl alcohols and methylene chloride); ketones (e.g., acetone); aromatic hydrocarbons such as benzene derivatives (e.g., xylenes and toluenes); lower molecular weight alkanes and cycloalkanes (e.g., hexanes, heptanes and cyclohexanes); and alkanoic acid esters (e.g., ethyl acetate, n-propyl acetate, isobutyl acetate, n-butyl acetate isobutyl isobutyrate, hexyl acetate, 2-ethylhexyl acetate or butyl acetate); and combinations and mixtures thereof.

Suitable co-solvents include polyhydric alcohols, which include glycols, triols and polyols such as ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol, trimethylene glycol, butylene glycol, polyethylene glycol, hexylene glycol, polyoxethylene, glycerin, trimethylpropane, sorbitol, polyvinylpyrrolidone, and the like.

Further suitable co-solvents include glycol ethers such as ethylene glycol monoethyl ether, glycol esters, glycol ether esters such as ethylene glycol monoethyl ether acetate and ethylene glycol diacetate; saturated and unsaturated fatty acids, mineral oil, silicone fluid, lecithin, retinol

derivatives and the like, and ethers, esters and alcohols of fatty acids.

Although the exact amount of co-solvents that may be used in the adhesive matrix composition depends on the nature and amount of the other ingredients, such amount typically ranges from about 0.1% to about 40%, and preferably from about 0.1% to about 30% by weight, and more preferably from about 1% to about 20%, by weight based on the dry weight of the total adhesive matrix composition.

In certain embodiments of the invention, a permeation enhancer is incorporated into the adhesive matrix composition. The term "permeation enhancer" as used herein refers to substances used to increase permeability and/or accelerate the delivery of an active agent through the skin or mucosa, and include monhydric alcohols such as ethyl, isopropyl, butyl and benzyl alcohols; or dihydric alcohols such as ethylene glycol, diethylene glycol, or propylene glycol dipropylene glycol and trimethylene glycol; or polyhydric alcohols such as glycerin, sorbitol and polyethylene glycol, which enhance drug solubility; polyethylene glycol ethers of aliphatic alcohols (such as cetyl, lauryl, oleyl and stearly) including polyoxyethylene (4) lauryl ether, polyoxyethylene (2) oleyl ether and polyoxyethylene (10) oleyl ether commercially available under the trademark BRIJ® 30, 93and 97 from ICI Americas, Inc., and BRIJ® 35, 52, 56, 58, 72, 76, 78, 92, 96, 700 and 721; vegetable, animal and fish fats and oils such as cotton seed, corn, safflower, olive and castor oils, squalene, and lanolin; fatty acid esters such as propyl oleate, decyl oleate, isopropyl palmitate, glycol palmitate, glycol laurate, dodecyl myristate, isopropyl myristate and glycol stearate which enhance drug diffusibility; fatty acid alcohols such as oleyl alcohol and its derivatives; fatty acid amides such as oleamide and its derivatives; urea and urea derivatives such

as allantoin which affect the ability of keratin to retain moisture; polar solvents such as dimethyldecylphosphoxide, methyloctylsulfoxide, dimethyllaurylamide, dodecylpyrrolidone, isosorbitol, dimethylacetonide, dimethylsulfoxide, decylmethylsulfoxide and dimethylformamide which affect keratin permeability; salicylic acid which softens the keratin; amino acids which are penetration assistants; benzyl nicotinate which is a hair follicle opener; and higher molecular weight aliphatic surfactants such as lauryl sulfate salts which change the surface state of the skin and drugs administered and esters of sorbitol and sorbitol anhydride such as polysorbate 20 commercially available under the trademark Tween® 20 from ICI Americas, Inc., as well as other polysorbates such as 21, 40,60, 61, 65, 80, 81, and 85. Other suitable enhancers include oleic and linoleic acids, triacetin, ascorbic acid, panthenol, butylated hydroxytoluene, tocopherol, tocopherol acetate, tocopheryl linoleate. If permeation enhancers are incorporated into the adhesive matrix composition, the amount typically ranges up to about 30%, and preferably from about 0.1% to about 15%, by weight based on the dry weight of the total adhesive matrix composition.

In addition to permeation enhancers, there may also be incorporated various pharmaceutically acceptable additives and excipients available to those skilled in the art. These additives include tackifying agents such as aliphatic hydrocarbons, mixed aliphatic and aromatic hydrocarbons, aromatic hydrocarbons, substituted aromatic hydrocarbons, hydrogenated esters, polyterpenes, silicone fluid, mineral oil and hydrogenated wood rosins. Additional additives include binders such as lecithin which "bind" the other ingredients, or rheological agents (thickeners) containing silicone such as fumed silica, reagent grade sand, precipitated silica, amorphous silica, colloidal silicon dioxide, fused silica,

silica gel, quartz and particulate siliceous materials commercially available as Syloid® , Cabosil® , Aerosil® , and Whitelite® , for purposes of enhancing the uniform consistency or continuous phase of the final composition. Other additives and excipients include diluents, stabilizers, fillers, clays, buffering agents, biocides, humectants, anti-irritants, antioxidants, preservatives, plasticizing agents, cross-linking agents, flavoring agents, colorants, pigments and the like. Such substances can be present in any amount sufficient to impart the desired properties to the carrier composition. Such additives or excipients are typically used in amounts up to 25%, and preferably from about 0.1% to about 10%, by weight based on the dry weight of the total adhesive matrix composition.

The adhesive matrix compositions according to the present invention can be prepared by first mixing appropriate amounts of the polymeric plastic material in volatile polar and/or non-polar organic liquids, such as those previously described as suitable volatile solvents. Appropriate amounts of active agent(s) are then added to the mixture together with appropriate amounts of pressure-sensitive adhesive(s), solvent(s) and/or co-solvent(s), with or without enhancer(s), and thoroughly mixed. The mixture of the adhesive matrix composition is next formed into a film at ambient temperature, preferably by coating or casting at a controlled specified thickness onto a flexible sheet material, such as a release liner, followed by evaporation of the volatile solvents at elevated temperatures (e.g., by passing through an oven). The non-volatile or higher boiling point solvents and/or co-solvents, such as the polyols, used in the carrier composition remain therein. The carrier composition has been coated or cast on the flexible sheet material, is then laminated to another flexible sheet material preferably a backing layer.

Appropriate size and shape individual transdermal drug delivery systems are cut and then packaged (e.g., pouched).

The order of steps, the amount of the ingredients, and the amount and time of mixing may be important process variables which will depend on the specific polymers, active agents, solvents and/or co-solvents, enhancers and additives and excipients used in the composition. These factors can be adjusted by those skilled in the art, while keeping in mind the objects of achieving a solubilized active agent and providing a uniform product that will also give desirable results.

Reference to FIG. 1 shows a matrix-type transdermal drug delivery system 10 comprising a pressure-sensitive adhesive matrix composition layer 11, a release liner 12, and a backing layer 13. Removal of the release liner 12 exposes the pressure-sensitive adhesive matrix composition for topical application to the user.

Further details and examples of pressure-sensitive adhesives, enhancers, solvents, co-solvents, release liners, backing layers, and other additives, as well as transdermal systems generally, suitable in practicing the invention are described in United States Patent Numbers 5,474,787 and 5,656,286, Serial Numbers 09/161,312 and 60/115,927, all of which are assigned to Noven Pharmaceuticals, Inc. and incorporated herein by reference.

EXAMPLES

The above description and following specific examples are hereby illustrative of pharmaceutically acceptable matrix compositions and transdermal drug delivery systems, and methods of making same, within the contemplation of the invention. The description and examples are in no way

intended to be, or should be considered, limiting of the scope of the invention. And while efforts have been made to ensure accuracy with respect to numbers used (such as amounts and temperatures), some experimental error and deviation should be accounted for and/or allowed.

Example 1

An estradiol/norethindrone acetate pressure-sensitive adhesive matrix composition was prepared by combining 0.7 parts of estradiol and 3.0 parts of norethindrone acetate along with 3.0 parts of ethyl cellulose (Ethocel® 10, Dow Chemical Corp., Midland, Michigan) in 30.0 parts ethyl acetate, 15.0 parts of toluene and 10.0 parts isopropyl alcohol. Then 12.2 parts of a polyacrylate adhesive (DURO-TAK® 87-2510; National Starch Company, Bridgewater, New Jersey) and 109.2 parts of a polysiloxane adhesive (BIO-PSA® Q7-4603; Dow Corning Corp, Midland, Michigan) were added and thoroughly mixed. Finally 9.0 parts of dipropylene glycol and 6.0 parts oleyl alcohol were added and mixed thoroughly in an appropriate container until the mixture was completely homogenous. The resulting composition had the ingredient concentrations on a dry weight percent basis (i.e., after evaporation of volatile solvents) as shown below.

INGREDIENT	DRUG WEIGHT %
Polysiloxane Adhesive (BIO-PSA® 7-4603)	66.3
Polyacrylate Adhesive (DURO-TAK® 87-2287)	5.0
Ethyl Cellulose (Ethocel® 10)	10.0
Dipropylene Glycol	9.0
Olelyl Alcohol	6.0
Estradiol	0.7
Norethindrone Acetate	3.0
	100.0

Examples 2-9

In the following examples, the method of Example 1 was used with the appropriate amounts of starting materials to yield compositions having the following ingredient concentrations set forth in tabular form in TABLE II. Examples 2, 3, and 5 are presented as control formulations for comparative purposes, but are not within the scope of the invention in as much as the resulting adhesive matrix compositions do not contain a polymeric plastic material.

TABLE II

	Ex.2	Ex.3	Ex.4	Ex.5	Ex.6	Ex.7	Ex.8	Ex.9
Polysiloxane Adhesive (BIO-PSA® 7-4502)	0.0	71.4	54.5	53.6	48.6	43.6	58.0	53.0
Polysiloxane Adhesive (BIO-PSA® 7-4603)	66.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Polyacrylate Adhesive (DURO-TAK® 87-2287)	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Polyacrylate Adhesive (Gelva® 788)	0.0	5.0	5.0	20.0	20.0	20.0	5.0	5.0
Ethyl Cellulose (Ethocel® 10)	0.0	0.0	15.0	0.0	0.0	0.0	10.0	15.0
Ethyl Cellulose (Ethocel® 20)	0.0	0.0	0.0	0.0	5.0	10.0	0.0	0.0
Poly vinyl pyrrolidone (KOLLIDON® 30)	0.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Polyvinylpyrrolidone (KOLLIDON® 90)	10.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dipropylene Glycol	9.0	6.0	6.0	8.0	8.0	8.0	8.0	8.0
Oleyl Alcohol	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Estradiol	0.7	1.6	3.5	2.4	2.4	2.4	3.0	3.0
Norethindrone Acetate	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

What is claimed is:

1. A transdermal delivery system for delivery of a therapeutically effective amount of an active agent comprising:

(a) a pharmaceutically acceptable pressure-sensitive adhesive matrix carrier composition,

(b) one or more polymeric plastic materials which are substantially insoluble in water in an amount up to 30%, said amount being sufficient to provide a substantially zero-order drug release profile in excess of 72 hours,

(c) one or more active agents,

(d) a crystallization inhibitor capable of absorbing and holding water, and

(e) optionally, one or more solvents, co-solvents and permeation enhancers.

2. The transdermal system according to claim 1, wherein the one or more insoluble polymeric materials are selected from the group consisting of celluloses, cellulose derivatives, polycarbonates, polystyrenes, alkylacrylates, polyvinyl chloride, polyurethanes and polyacrylonitrile.

3. The transdermal system according to claim 2, wherein the cellulose derivatives are cellulose esters and cellulose ethers.

4. The transdermal system according to claim 3, wherein the cellulose ethers are ethyl cellulose polymers.

5. The transdermal system according to claim 3, wherein the cellulose esters are selected from the group consisting of cellulose acetate, cellulose acetate butyrate, cellulose acetate phthalate and cellulose acetate propionate.

6. The transdermal system according to claim 1, wherein the solvents and co-solvents are polyhydric alcohols.

7. The transdermal system according to claim 1, wherein the pressure-sensitive adhesive matrix carrier is a blend of a polyacrylate adhesive and a polysiloxane adhesive.

8. The transdermal system according to claim 1, wherein the crystallization inhibitor is polyvinylpyrrolidone.

9. The transdermal system according to claim 1, wherein the one or more active agents are selected from the group consisting of steroidal and hormonal agents, analgesics and anti-migraine agents, anesthetics, anti-inflammatory and corticoid agents, central nervous system stimulants and agents, cardioactive agents, anti-Parkinson's and anti-Alzheimer's agents, anti-psychotic agents, anti-anxiety agents, anti-depressants, anxiolytic agents, sedatives, hypnotics, anti-microbial agents, and anti-cancer agents.

10. The transdermal system according to claim 9, wherein the steroidal and hormonal agents are selected from the group consisting of ethinyl estradiol, progesterone, norethindrone, norethindrone acetate, norethisterone, methyltestosterone, testosterone, and mixtures thereof.

11. The transdermal system according to claim 10, wherein the estradiol is 17 β-estradiol.

12. The transdermal system according to claim 1, comprising about 10% - 40% polyacrylate adhesive, about 30% - 60% polysiloxane adhesive, about 2% - 10% dipropylene glycol, about 1% - 10% oleyl alcohol, about 5% - 20% ethyl cellulose, about 5% - 15% polyvinylpyrrolidone and about 1% - 5% 17 β-estradiol by weight based on the dry weight of the total composition.

13. The transdermal system according to claim 1, comprising about 3% - 25% polyacrylate adhesive, about 30% - 70% polysiloxane adhesive, about 5% - 15% dipropylene glycol, about 1% - 10% oleyl alcohol, about 5% - 15% polyvinylpyrrolidone, about 1% - 15% ethyl cellulose, about 0% - 15% cellulose acetate butyrate, about 0% - 15% cellulose acetate propionate, about 0.1% - 5% 17 β-estradiol, and about 1% - 7% norethindrone acetate by weight based on the dry weight of the total composition.

14. A method of prolonged transdermal administration of a therapeutically effective amount of one or more active agents to a subject comprising the steps of:

(a) providing the transdermal system of claim 1, and

(b) topically applying the transdermal system to administer the one or more active agents.

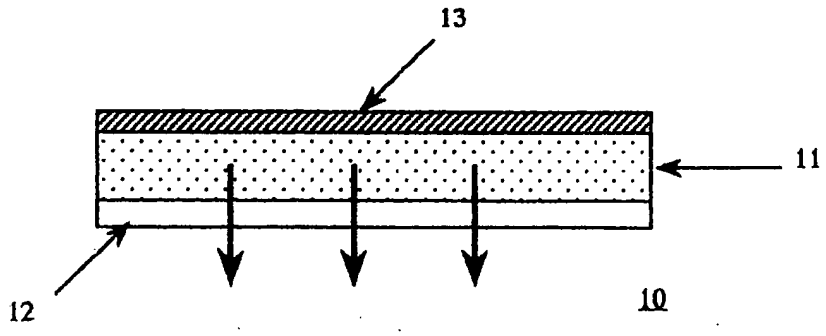


FIG. 1

FIGURE 2

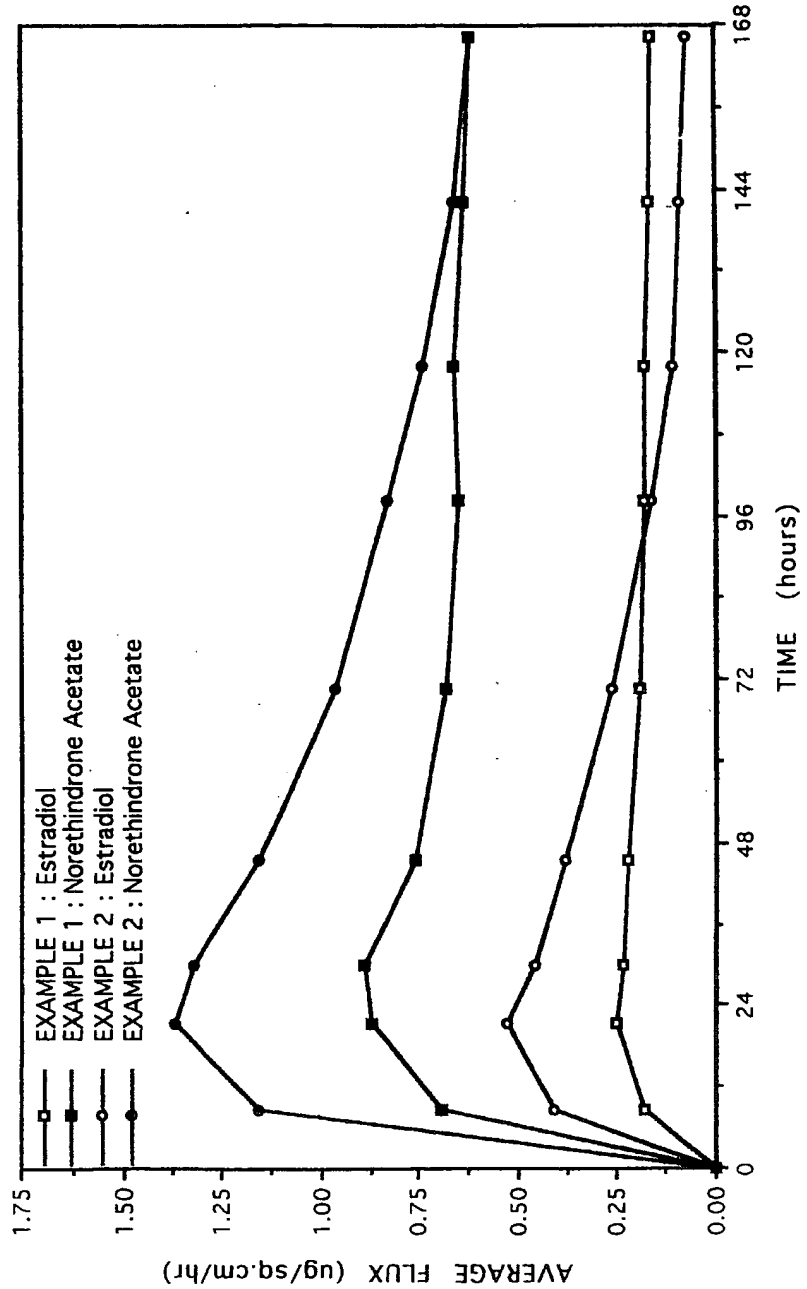

EXAMPLE 1 : Estradiol
EXAMPLE 1 : Norethindrone Acetate
EXAMPLE 2 : Estradiol
EXAMPLE 2 : Norethindrone Acetate
AVERAGE FLUX (ug/sq.cm/hr)
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
24
48
72
96
120
144
168
TIME (hours)

FIGURE 3

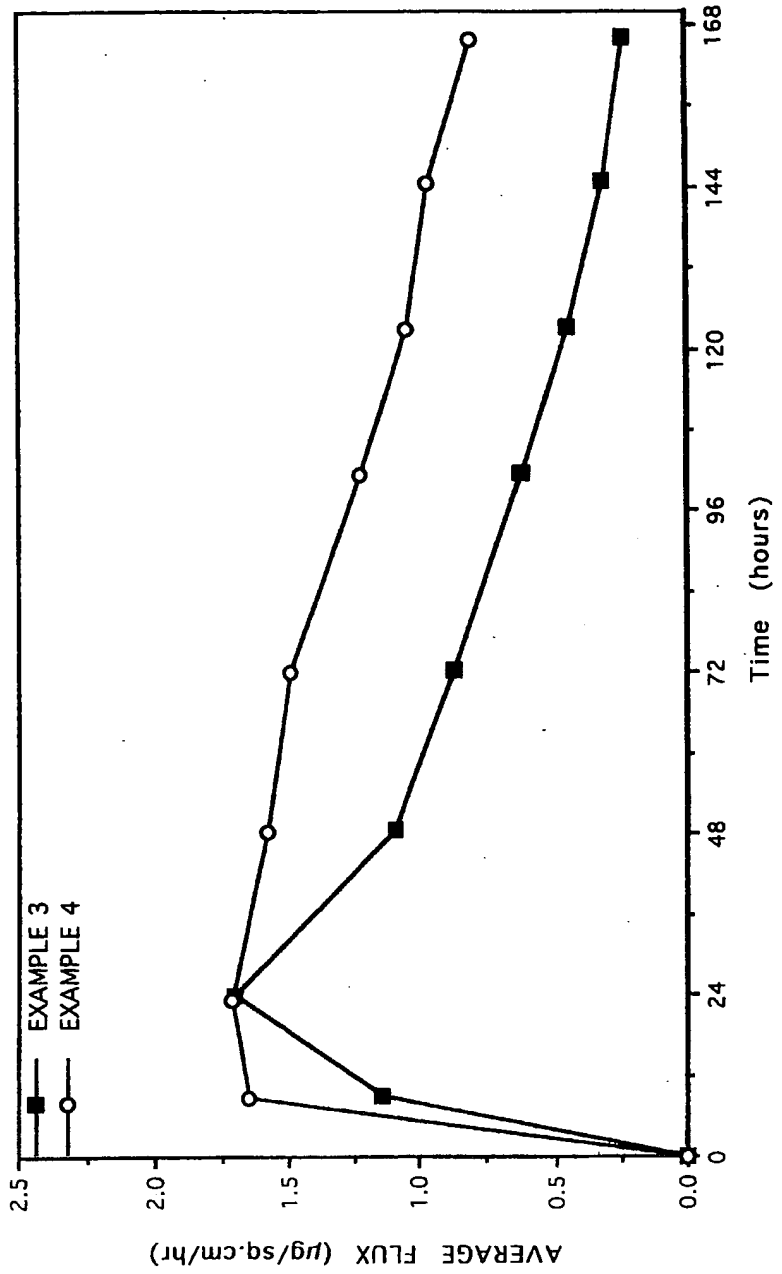

AVERAGE FLUX (μg/sq.cm/hr)
2.5
2.0
1.5
1.0
0.5
0.0
0
24
48
72
96
120
144
168
Time (hours)
EXAMPLE 3
EXAMPLE 4

FIGURE 4

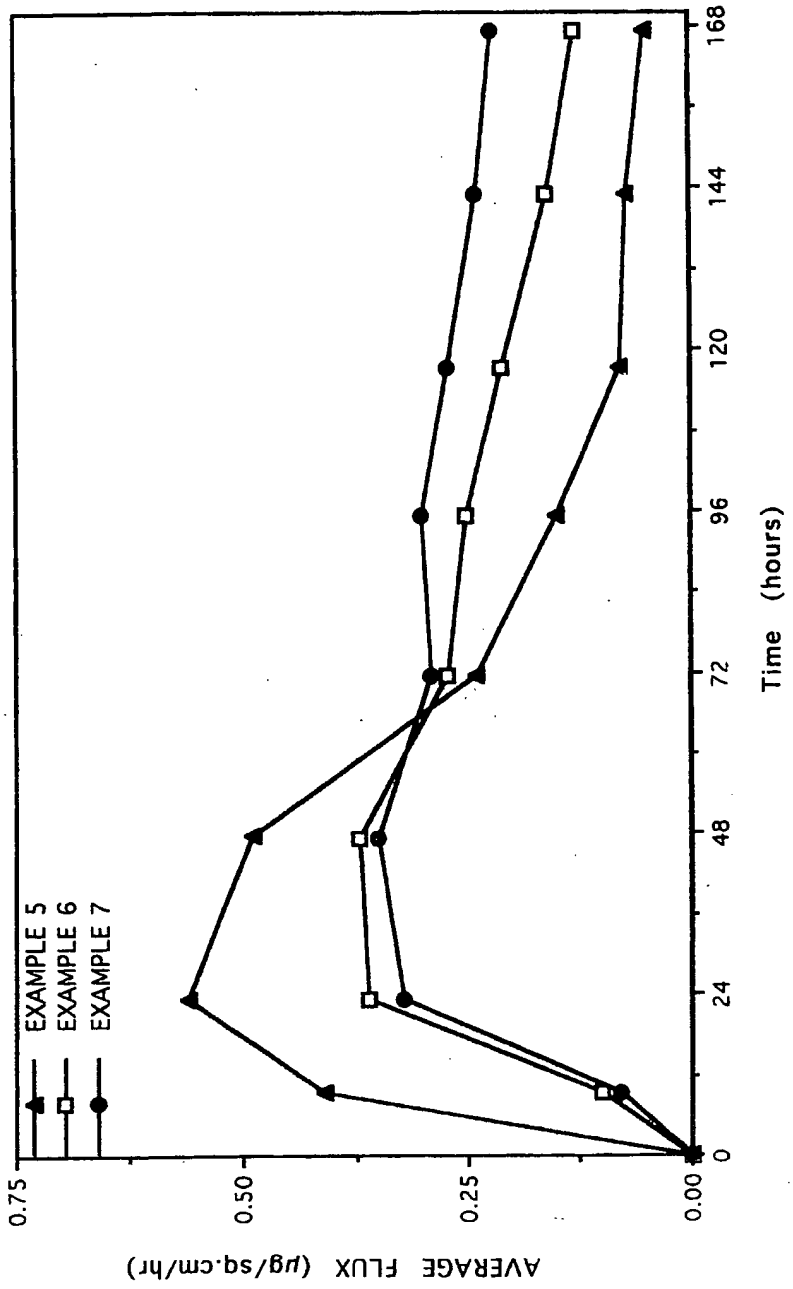

EXAMPLE 5
EXAMPLE 6
EXAMPLE 7
0.00
0.25
0.50
0.75
AVERAGE FLUX (μg/sq.cm/hr)
0
24
48
72
96
120
144
168
Time (hours)

FIGURE 5

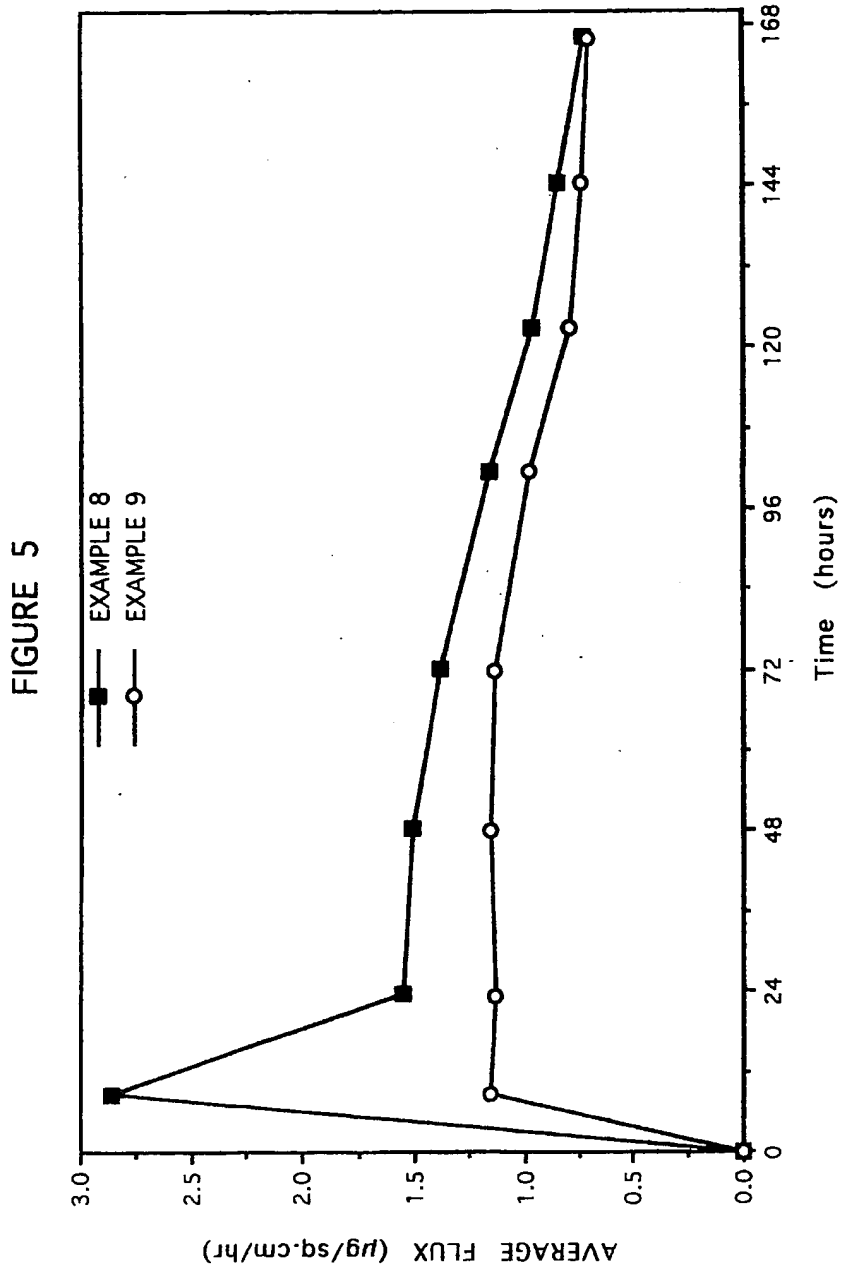
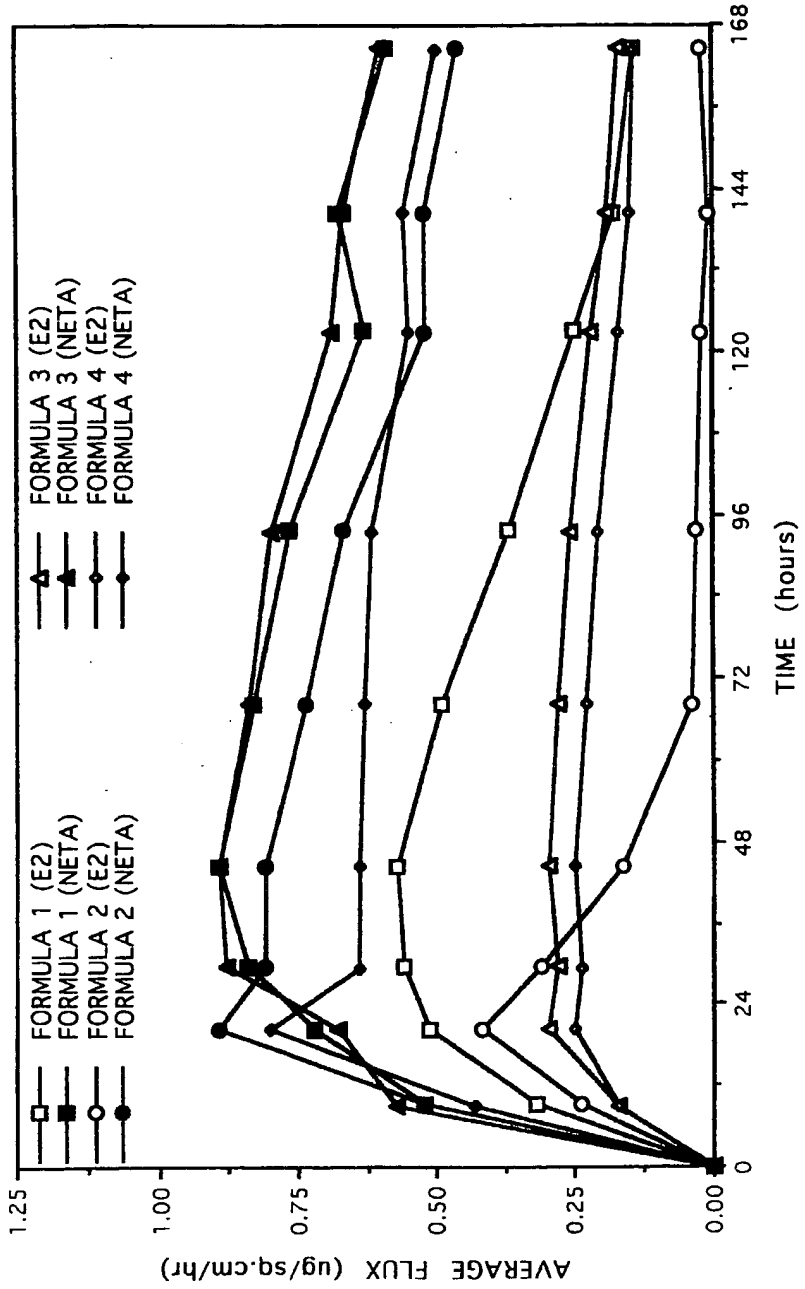

EXAMPLE 8
EXAMPLE 9
AVERAGE FLUX (µg/sq·cm/hr)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
24
48
72
96
120
144
168
Time (hours)

FIGURE 6


FORMULA 1 (E2)
FORMULA 1 (NETA)
FORMULA 2 (E2)
FORMULA 2 (NETA)
FORMULA 3 (E2)
FORMULA 3 (NETA)
FORMULA 4 (E2)
FORMULA 4 (NETA)
AVERAGE FLUX (ug/sq.cm/hr)
1.25
1.00
0.75
0.50
0.25
0.00
0
24
48
72
96
120
144
168
TIME (hours)